American Academy of Dermatology Association

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1051
Rockville, MD 20857

To Whom It May Concern:

The American Academy of Dermatology Association would like to take this opportunity to share with you our comments regarding the guidance for industry, "Acne Vulgaris: Developing Drugs for Treatment." We appreciate the opportunity to share with you our strong concerns with the guidance as issued.

It is our opinion that this document contains substantive errors regarding acne and the evaluation of acne therapies, and if these guidelines are adopted in their present form, the development and approval of new acne therapies will be severely hampered thus depriving our patients of improved therapy for this widespread disease. The AADA strongly recommends that these guidelines not be adopted.

Should you have any questions or would like to discuss these comments in more detail, please contact Vera LeBrun at vlebrun@aad.org or 202-842-3555.

Sincerely,

Clay J. Cockerell

Clay J. Cockerell, MD
President

CJC/vel

Enclosure

cc: David M. Pariser, MD, Secretary
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The American Academy of Dermatology Association, with the assistance of a number of leaders within dermatology in the fields of acne research and clinical practice, would like to take this opportunity to share with the FDA our assessment of the guidance for industry, "Acne Vulgaris: Developing Drugs for Treatment (Docket No. 2005D-0340, CDER 2004129)." It is our opinion that this document contains substantive errors regarding acne and the evaluation of acne therapies, and if these guidelines are adopted in their present form, the development and approval of new acne therapies will be severely hampered thus depriving our patients of improved therapy for this widespread disease. The AADA strongly recommends that these guidelines not be adopted.

The document shows a poor understanding of the pathophysiology and clinical expressions of acne vulgaris. Line 65 states closed comedones may be precursors to large inflammatory lesions. This is incorrect. Closed comedones rarely become inflammatory lesions. Rather, a microscopic, pre-clinical lesion – the microcomedo – is the precursor to both comedones and inflammatory lesions. Nodules are 1cm in diameter and greater, not 0.5 cm. Large papules greater than 5 mm exist in patients who do not have the most severe inflammatory form of acne—nodulocystic acne. Nodulocystic acne is not defined as a patient with greater than 2 nodules. Rather widespread, numerous nodular lesions in association with large papules and/or pustules are seen in this type of acne.

In line 121 it is stated that use of a vehicle/placebo control is desirable for acne studies. The AADA is concerned that this is an inappropriate burden for subjects with the severest forms of acne. Denying a patient therapy in the interest of maintaining a control group is scientifically sound but ethically questionable. We suggest that the severest forms of acne be studied using a standard comparator active agent.

The document presents an investigator's global assessment (IGA) grading scale for acne severity and proposes that this scale be used as a primary end point in assessing the efficacy of a new therapy. The proposed scale encompasses clear skin (non-acne) and mild disease and differs from the grading scale currently recommended by the FDA. Our objections to the new proposed IGA scale are as follows:

a) Grade 0 & 1 are the same in that "total absence of lesions" versus "1 papule and a rare comedo" are indistinguishable on clinical grounds and fail to meet the FDA recommendations on line 349 that grades be defined "unambiguously" to represent each severity grade.
b) Grade 2 – "some non-inflammatory lesions" with "no more than a few inflammatory lesions" describes a patient who is in our opinion almost clear.
c) Moderate severity – "many non-inflammatory lesions" and "may have some inflammatory lesions" is a description of mild, not moderate acne. Patients with moderately severe inflammatory acne typically will have more than 20 to 35 inflammatory lesions and not "some".
d) Severe – the description is that of moderate inflammatory disease.
e) The proposed scale of 0 to 4 encourages only mild to moderate inflammatory acne and does not include patients with more severe inflammatory acne who should not be categorized as nodulocystic acne. Use of this scale would preclude the study of moderately severe to severe inflammatory acne. In addition, this scale would result in industry defining patient populations with mild inflammatory acne in order to have a chance of achieving a successful outcome. The FDA document in fact recognizes this and so stated in lines 137-139.
f) The proposed IGA scale is heavily weighted towards the assessment of inflammatory acne lesions and as such is totally inappropriate for evaluating a drug with potential benefit only in the non-inflammatory phase

of acne. This becomes a critical issue in that there are now options to seek an indication for inflammatory acne, non-inflammatory acne or both.

g) Moreover development of an IGA scale for non-inflammatory acne or for implementing the proposed scale for draft in the Guidance document is problematic in that the draft proposal suggests that each company should validate its global assessment before implementation. This proposal creates a catch-22 in that an IGA is required but first must be validated. If it cannot be validated, then a clinical study cannot proceed. There should be at least one prior successful validation either by the agency or by academia before any requirement for an IGA is implemented.

In addition to finding the proposed scale to be deficient in describing various "grades of acne" we are opposed to using an Investigators Global Assessment (IGA) as a primary end point for judging efficacy for the following reasons:

a) We agree with the FDA that there is no standardized and reproducible grading system for the severity of acne (line 80) and that it is more subjective than lesion counts (line 144 & 145) and has a high degree of variability (line 303).

b) For the above reasons, it was the recommendation of the Dermatology Advisory Committee (Nov. 2002) and the invited speakers that an IGA <u>not</u> be a primary end point in assessing efficacy of anti-acne drugs. We note that the Generic Division of the FDA has taken that advice and now uses the IGA as a secondary end point. We urge the Dermatology Division to do likewise. Furthermore in that two-day meeting, the FDA presented their analysis of previously submitted data and made the point that successful reduction in lesion counts was most clearly seen in those with higher lesion counts while clinical success using an IGA scale was seen in those with mild inflammatory acne. This disconnect is unsound from a clinical point of view.

c) The Guidance document states that an IGA is necessary in order to capture an appreciation of the size of lesions, intensity of inflammation and location of lesions. Interestingly, the proposed IGA makes no comment on these aspects of inflammation. Furthermore, the FDA comments that describing lesion counts does not give an overall view of improvement for patients with a range of baseline counts. This is true for the proposed change of using actual counts rather than percent change. The latter gives a clear view of degree of improvement, has been the method for analysis for more than 25 years and is understood by dermatologists. The Guidance document provides no comment on why a change from percent change to actual lesions count is proposed.

d) The proposal for IGA grading is giving an imprecise method equal weight with a precise method. Lesion counting is precise and unequivocal. IGA is essentially a *gestalt* method of acne grading that is subject to inter-investigator variability and is purely subjective. The proposed change is equivalent to having hypertension measured by automated monitors and manual palpation and weighting both equally in testing a new drug.

The Guidance document recommends a minimum of 12 week study for Phase III trials (current standard) with a "follow-up" period to evaluate recurrence following treatment discontinuation (lines 109-110). The "follow-up" recommendation makes no sense in that it is not in line with the natural history of acne. No acne therapies, including isotretinoin, are able to induce a remission of acne when given for a 12-week period, particularly as single agents. Acne is a chronic disease and those with >20 inflammatory and 30 non-inflammatory lesions (current FDA requirement) will be expected to "relapse" within a month. Having these patients remain in a follow-up period without treatment may be unethical.

Another recommendation which seems unreasonable and unnecessary is the need to re-establish the contributions of individual ingredients to a fixed combination when a "new formulation" is studied. The current system of showing non-inferiority of a new formulation to the original combination is a well established method that should be maintained.

The Guidance document calls for companies to develop a photographic documentation of each subject's improvement for Agency "auditing purposes" (line 357). There currently is no standardized photographic methodology for visualizing comedones, particularly closed comedones which the Agency agrees are hard to see even when viewing a patient head on (lines 64, 65). At the November 2002 Dermatological Advisory Committee, there was discussion about development of a photographic methodology to complement lesion counting. We urge the Agency not to ask for photographic documentation until a methodology visualizing non-inflammatory comedones is developed.

In sum, the AADA concludes that there are substantive errors in the proposed Guidance document. It is our judgment that these errors will result in serious impediment to the development of new therapies, particularly for moderately severe and severe inflammatory acne. For these reasons, we urge the FDA not to implement the proposed Guidance. The American Academy of Dermatology Association is willing and interested in working with the FDA to adopt meaningful and effective guidelines. Please contact Vera LeBrun in our Washington Office at vlebrun@aad.org or 202-842-3555 if you have questions arising from our comments or if you would like to discuss the issue further. Thank you.